REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 26, 27, 29, 30 and 32 are pending after entry of the amendments set forth herein.

Claims 26-27 and 29-32 were examined and rejected.

Claims 27, 29 and 32 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to the claims is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 8 lines 1-4. Accordingly, no new matter is added.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection of claim 27 under 35 U.S.C. §112, first paragraph (written description)

In paragraph 5 of the Office Action, claim 27 is rejected for not satisfying the written description requirement of 35 U.S.C. §112, first paragraph.

Claim 27 is also rejected based on similar or the same grounds under 35 U.S.C. §112, first paragraph, for not satisfying the written description requirement of 35 U.S.C. §112, first paragraph, in paragraph 11 of the Office Action.

Rather than address this rejection twice, the rejection will be addressed only once, in the section entitled "**Rejection under 35 U.S.C. §112, first paragraph (written description)**", below.

Claim rejections under 35 U.S.C. §§ 101 and 112 – lack of utility / enablement

Claims 26-27 and 29-32 are rejected under 35 U.S.C. § 101 as having no supported specific, substantial and credible utility, or, in the alternative, a well-established utility. Further, because the Office has deemed that the claimed subject matter lacks utility, the claims are also rejected under 35 U.S.C. § 112 (enablement) since a skilled person would assertedly not know how to use the claimed invention.

The basis of this rejection is that there is assertedly no teaching or evidence in the specification or in the art of record that any of the encoded proteins are in any way associated with apoptosis. The Applicants respectfully traverse these rejections together.

First, as a point of law, Applicants note that the Office has based the rejection of these claims on the grounds that they are assertedly not supported by "a specific asserted utility, a well-established established utility, or a substantial utility" (see, e.g., Office Action, page 4, item 6). However, the Guidelines for Examination of Applications for Compliance with the Utility Requirement (Federal Register Vol 66 No. 4, Jan 5, 2001), "The Utility Guidelines", to which Examiners must follow in determining utility, states that the standard for satisfying 35 U.S.C. § 101 is a "specific, substantial and credible utility" ***or*** a "well established" utility (see page 1098, column 1 of the Utility Guidelines). As such, the Office appears to have used a incorrect standard for formulating this rejection.

However, since this rejection appears to be founded in the Office's assertion that there is no evidence linking ING2 to apoptosis, Applicants have interpreted this rejection as meaning that the credibility of the utility of the claimed invention is being questioned by the Office.

In response to this rejection, Applicants respectfully submit that experimental evidence showing that ING2 proteins are associated with apoptosis is found in the results shown in Figure 3 of the instant specification. This figure depicts the results of p53 activation assays, in which three isoforms of ING2 (ING2A, ING2B and ING2C) are individually tested for p53 activation. The results shown in this figure are very clear: ING2 proteins activate p53. p53 is a well known inducer of apoptosis. It reasonably follows that ING2 proteins activate an inducer of apoptosis. In contrast to the Office's assertions, there is evidence in the specification that any of the encoded proteins are associated with apoptosis: they induce an activator of p53, a known inducer of apoptosis.

Therefore, in view of the data provided by Figure 3 of the instant application, a skilled person would recognize that the claimed invention, which is directed towards ING2 proteins having a sequence that is similar to or the same as that set forth in SEQ ID NO:8, has a credible, specific, and substantial utility.

The Applicants respectfully submit that this rejection has been adequately addressed by the remarks set forth above. Accordingly, this aspect of the rejection may be withdrawn.

In view of the foregoing discussion, withdrawal of these rejections are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claims 27 and 31-32 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office asserts that the specification does not provide adequate enablement of polypeptide variants having at least 90% sequence identity to the recited sequence, SEQ ID NO:8. The basis of this rejection is the Office's assertions that the function of biological molecules is unpredictable, and changes made to biological molecules have unpredictable effects.

The Applicants respectfully traverse this rejection.

Solely to expedite prosecution and without any intent to acquiesce to this rejection, the claims are amended to recite polypeptides having at least *95%* sequence identity to the contiguous sequence set forth in SEQ ID NO:8.

The Applicants respectfully submit that a person of ordinary skill in the art (referred to herein for brevity's sake as the "skilled person") would find ample guidance in the specification to make and use such variants having at least 95% sequence identity to a disclosed polypeptide or polynucleotide without undue experimentation. Reasoning in support of the Applicants' submission is set forth below.

For convenience's sake, polynucleotides and polypeptides having at least 95% sequence identity to SEQ ID NO:8 are referred to as "ING2 variants".

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

With respect to the instant claims, therefore, the question is: could one of skill in molecular biology, described herein as a "skilled person", in view of the instant specification and information that is already known, make ING2 variants and use them without undue experimentation? The answer to this question, for the reasons set forth below, is an unequivocal "yes".

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1 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

Applicants have provided several examples of variants in their working examples

In the instant specification, the sequences of a total of five ING2 isoforms, ING2A, ING2B, ING2C, ING2D and ING2E (corresponding to SEQ ID NOS: 2, 4, 6, 8 and 10, respectively) are described. ING2A, ING2B, ING2C and ING2E show 87.6% identity, 94.2% identity, 94.2% identity, and 81.8% to ING2D (corresponding to SEQ ID NO:8), respectively.

All of these polypeptides were identified in a two-hybrid binding assay using IAP protein as a bait and three of these sequences, ING2A, ING2B, ING2C, were tested in p53 induction assays. These sequences caused induction of p53, either separately, or in combination with p53. Accordingly, these assays demonstrate that ING2 variants that have as little as 81.8% sequence identity to SEQ ID NO:8 can bind IAP and can induce p53.

Considering that ING2 isoforms having as little as 81.8% identity to each other can effectively can bind IAP and can induce p53, a skilled person would reasonably expect ING2 variants with *at least 95% identity* (i.e., significantly greater than 81.8% identify) to SEQ ID NO:8 to have an activity similar to that of SEQ ID NO:8.

Applicants have provided adequate guidance as to which amino acids can be modified in an ING2 protein to maintain function

The Applicants respectfully submit that they have provided adequate guidance with respect to ING2 protein domains important for ING2 function and which particular amino acids should or should not be altered to making functional ING2 variants.

With regard to ING2 protein domains that are important for ING2 function, a skilled person would look towards Fig. 11 of the specification, and what is known in the art about the structure of the ING1 protein, which is shown aligned with the subject ING2 isoforms in Fig. 11, for guidance.

Fig. 11 shows an alignment of the subject ING2 isoforms with other ING proteins, including ING1. Highlighted by in black boxes are residues that are conserved between two or more proteins shown in this alignment. This alignment therefore shows several regions that are conserved between the various ING proteins, including, in particular, several conserved amino acids at the C-terminus of the protein, and a large region of amino acids at the C-terminus of the protein, starting from the DPNEPTY… and finishing at …..TTKPKGKW.

Since ING1 and ING2 are functionally similar and contain several regions of conserved amino acids, including a large block of conserved amino acids at their C-termini, a skilled person would instantly recognize that these domains may be important for function of ING proteins. Moreover, the fact that these domains are conserved among the different ING2 isoforms themselves further suggests to the skilled person that these domains are less preferred for introduction of amino acid changes, particularly those non-conservative amino acid changes. A skilled person would generally avoid making amino acid changes in these regions when designing ING2 variants that are at least 95% to SEQ ID NO:8.

With the knowledge that ING1 and ING2 have apoptosis activity and have conserved domains, a skilled person would, for example, swap domains from ING1 to ING2 (i.e. SEQ ID NO:8) with an expectation that the resultant protein would retain an apoptosis activity.

Further, a skilled person, upon viewing the instant specification, particularly Figure 11, when preparing for assays using SEQ ID NO:8 variants, would have knowledge of the prior art regarding the structure/function relationship of ING proteins. The skilled person would have knowledge of several papers on the structure/function relationship of ING1 proteins. In particular, Zeremski (JBC 274:32172-32181, 1999; copy enclosed as Exhibit A), discusses several amino acids that are conserved between ING proteins (see Fig. 4B on page 32177 and abstract), and indicates that the conserved C-terminal domain is a "PHD" DNA binding domain (see page 32180, second column). Most of the conserved amino acids of Zeremski's sequence alignment are also indicated as being conserved in the alignment of Fig. 11. While not relied upon to make this assertion, Zeremski confirms the conserved amino acids identified in Fig. 11, and gives a domain name and function to the conserved C-terminal region.

The instant specification provides significant guidance as to which amino acids could be changed in an ING2 variant having the sequence of SEQ ID NO:8 in order for it to remain functional.

With regard to particular amino acid alterations, a skilled person would look towards the sequence alignment shown in Fig. 11, as well what is known in the art about the structure of the ING1 protein, for guidance.

The bottom line of the ING sequences shown in Figure 11 shows a "consensus" sequence. This consensus sequence shows amino acids that are conserved in all ING proteins shown (indicated in upper case letters). Residues conserved in more than two ING proteins (but not all ING proteins) are shown in

lower case letters. Since all the ING proteins shown in the figure have a conserved function, a skilled person would recognize that in order to make ING2 variants, in general, amino acids at positions that correspond to upper case letters in the consensus sequence should not be modified (and certainly at least not modified by non-conservative amino acid substitution), and that amino acids that correspond to lower case letters in the consensus sequence may be modified to any other amino acid at that position, for example. Further, at positions in which there is no amino acid listed in the consensus sequence, a skilled person may be able to choose any amino acid at that position. A skilled person would recognize that, for example, at positions in which D and E are the only amino acids present, either D or E may be used at that position; at positions in which K or R are the only amino acids present, either D or R may be used at that position; at positions in which S or T are the only amino acids present, either S or T may be used at that position, and at positions in which L, I or V are present, either L, I or V may be used at that position, etc.

In other words, by simply looking at the sequence alignment shown in Fig. 11, a skilled person would instantly recognize a large number of amino acids in an ING2 protein having the sequence of SEQ ID NO:8 that may be substituted, and reasonably expect that these substitutions would have no significant effect on its function.

Applicants respectfully submit that a skilled person, in addition to finding guidance for which amino acids are alterable, would find guidance for acceptable amino acid substitutions. Applicants further submit that a skilled person, without any undue experimentation, can alter the sequence of an ING2 isoform without significantly affecting its activity.

In summary, since ING proteins that have as little as 81.8% identity to an ING2 protein have a similar function as ING2 proteins, a skilled person would recognize that ING proteins with at least 95% sequence identity to an ING2 protein could be made and used without undue experimentation. The specification teaches it is possible to substantially modify the amino acid sequence of an ING2 protein, to make an ING2 variant that is suitable for binding to IAP. A skilled person, in deciding which amino acids may be changed to make such variants, would look to the teachings of Fig. 11 of the instant specification, where suitable amino acid substitutions may be identified.

Applicants are aware that biological systems can, in certain circumstances, be unpredictable. However, Applicants respectfully submit that in the instant case, two different ING proteins with as little

as 81.8% sequence identity bind IAP and exhibit p53-inducing activity. Furthermore, suitable amino acid changes are suggested in the teachings of Fig. 11. Thus the skilled person would find it reasonable to conclude that the suggested amino acid changes to the instant ING2 proteins have a predictable effect upon ING2 protein activity.

Furthermore, Applicants note that in order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the Office is reminded that extensive experimentation may be performed, so long as the experimentation is routine, and that every species within a genus does not have to be operative for a claim to be fully enabled.[2]

The Applicants note that methods for determining which ING2 variants bind to IAP, e.g., two hybrid assays, etc., are described in detail in the specification. As such, the Applicants respectfully submit that only IAP binding ING2 variants are claimed, and that determining which ING2 variants bind IAP requires only routine experimentation, not undue experimentation.

In view of the foregoing, the Applicants respectfully submit that a skilled person would be able to design and make variants of the instant ING2 proteins that are at least 95% identical to the claimed ING2 protein, without any undue experimentation.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph (written description)

Claims 27 and 30-32 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed polypeptides. Specifically, the Office Action asserts that the specification provides an inadequate

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[2] *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985). *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

description of the polypeptide having at least 90% sequence identity to SEQ ID NO:8. The Applicants respectfully traverse this rejection.

Solely to expedite prosecution and without any intent to acquiesce to this rejection, the claims are amended to recite polypeptides having at least *95%* sequence identity to the contiguous sequence set forth in SEQ ID NO:8.

The guidance set forth in the "Synopsis of Application of Written Description Guidelines", as published to the world wide website of the U.S.P.T.O. on March 1st, 2000 (http://www.uspto.gov/web/offices/pac/writtendesc.pdf), indicates that the claims are adequately described.

Example 14 of the Synopsis describes a scenario that is very similar to that currently under examination. Example 14 provides an example of a specification that discloses the sequence of a polypeptide having the sequence of SEQ ID NO:3, and also discloses that the polypeptide has a certain activity. This example also states that the specification also "contemplates but does not exemplify" variants of SEQ ID NO:3, and provides an assay for measuring the activity of the protein. In this example, the claims are directed to polypeptides having a sequence that is at least 95% identical to that of SEQ ID NO: 3 and catalyze the reaction of A→B.

The Synopsis states that the claimed subject matter is adequately described by the specification and the requirements of 35 USC §112 first paragraph have been met because "The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity."

For the Examiner's convenience, Example 14 of the Synopsis of Application of Written Description Guidelines is reproduced below:

Example 14: Product by Function

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of **A B.** The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates

that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:
A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3.

Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species.

The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed

by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

The Applicants respectfully submit that the fact pattern of the example set forth above is very similar to the instant fact pattern. In other words, the instant specification a) describes the sequence of a full length polypeptides (to be more exact, SEQ ID NO:8), b) describes that SEQ ID NO:8 has IAP binding activity, c) "contemplate but does not exemplify" variants of SEQ ID NO:8 (excluding SEQ ID NOS: 2, 4, 6 and 10), and d) provides detailed methods of IAP binding activity can be assayed (see e.g., page 42, lines 16-27 of the instant specification).

As such, by the reasoning set forth in the Example 14 of the Synopsis, the instant claims should be considered adequately described by the specification, meeting the requirements of 35 USC §112, first paragraph.

Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §102

Claims 31 and 32 is rejected under 35 U.S.C. §102(b) as being anticipated by a variety of sequences deposited in the Genbank database.

Without acquiescing to the correctness of this rejection, claim 32 has been amended to recite an isolated protein having the *contiguous* amino acid sequence set forth in SEQ ID NO:8. Since none of the cited sequences have the *contiguous* amino acid sequence set forth in SEQ ID NO:8, they cited sequences cannot anticipate the subject matter of the claim.

Claim 31 is cancelled and therefore this rejection is moot with respect to claim 31.

In view of the foregoing discussion, withdrawal of this rejection is respectfully requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RIGL-008CIP.

Respectfully submitted,
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